UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,668	01/06/2000	GARY A. BANNON	HS-102-DIV	1978

7590 10/21/2004

Brenda Herschbach Jarrell
Choate, Hall & Stewart
Exchange place
53 State Street
Boston, MA 02109

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/478,668
Filing Date: January 06, 2000
Appellant(s): BANNON ET AL.

Charles E. Lyon D Phil.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/2/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

Claims 37-51, 53 and 60-71 are pending and on appeal.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct. Examples 1-2 correspond to page 16 and page 24, respectively. Examples 3-4 are shown on page 28. Example 5 corresponds to page 29 of the specification.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that:

(1) the enablement Rejection under 35 U.S.C. § 112 first paragraph of claims 37-51, 53 and 65-71 (Group A) stands or falls together; claims 60-62 and 65-71 (Group B) and claims 63-64 and 65-71 (Group C) stand or fall together.

(2) The written description Rejection under 35 U.S.C. § 112 first paragraph of claims 37-51, 53 and 65-71 (Group A) stands or falls together; claims 60-62 and 65-71 (Group B) stand or fall together; and the claims 63-64 and 65-71 (Group C) stand or fall together.

(3) The new matter rejection under 35 U.S.C. § 112 first paragraph of Claims 65-69 stand or fall together;

(4) Claims 37, 60 and 63 rejected under 35 U.S.C. 112 second paragraph of stand or fall together.

(5) Claims 37-39, 41-46, 48-51 and 53 rejected under 35 U.S.C. § 102(b) of stand or fall together.

(6) Claims 37, 60-61 and 63-71 rejected under 35 U.S.C. § 102(a) stand or fall together.

(7) Claims 37 and 47 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat No. 5,547,669 (Aug 1996) in view of Hoyne et al (Immunology and Cell Biology 74: 180-186, 1996) stand or fall together.

(8) Claim 37 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat No. 5,547,669 (Aug 1996) in view of Burks et al (J. Allergy Clin Immunol. 693(4): 743-50, 1994) stands or falls alone.

(9) Claims 60-62 stand or fall together under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat No. 5,547,669 (Aug 1996) or Burks et al (J. Allergy Clin Immunol. 693(4): 743-50, 1994) each in view of U.S. Pat No. 5,547,669 (Aug 1996) and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

However, it is the examiner's position that the enablement and written description rejections of claims 37-51, 53 and 65-71 should stand or fall together because claims 65-71 are in Groups A, B and C. Claims 37-51, 53, and 60-71 were rejected under enablement and written description.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix I to the brief is correct.

(9) Prior Art of Record

5,547,669	Rogers	08-1996
5,449,669	Metcalfe	09-1995

Fasler *et al*, J. Allergy and Clinical Immunology 101(4 pt 1): 521-30, April 1998.

Burks *et al*, Eur. J. Biochem. 245: 334-339, April 1997.

Stanley *et al*, Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997.

Skolnick *et al*, Trends in Biotech. 18(1): 34-39, Jan 2000.

Colman *et al*, A structural view of immune recognition by antibodies, pages 33-36, 1994.

Hoyne *et al*, Immunology and Cell Biology 74: 180-186, 1996.

Burks *et al*, J. Allergy Clin Immunol. 693(4): 743-50, 1994.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 first enablement

Claims 37-51, 53, and 60-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a modified *peanut* protein allergen selected from the group consisting of Ara h1, Ara h2 and Ara h3 whose amino acid sequence is identical to that of an unmodified protein allergen such as the ones except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut protein allergen such as the ones shown in page 24, Table 4-6 (pages 26-27); (2) the modified peanut protein allergen mentioned above wherein the at least one IgE epitope is one that is recognized when the unmodified peanut allergen is contacted with a pool of sera IgE taken from a group of at least of two individuals that are allergic to the unmodified peanut protein allergen; (3) the modified peanut protein allergen mentioned above wherein at least one modified amino acid is located in the center of the at least one IgE epitope; (4) the modified peanut protein allergen mentioned above wherein at least one IgE epitope of the unmodified protein allergen has been modified by substitution; (5) the modified peanut protein allergen mentioned above wherein at least one amino acid in the at least one IgE epitope of the unmodified protein allergen has been substituted by a neutral or hydrophilic amino acid; (6) the modified peanut protein allergen mentioned above wherein the modified peanut protein allergen retains the ability to activate T cells; (7) the modified peanut protein allergen mentioned above wherein the modified peanut protein allergen retains the ability to bind IgG; (8) the modified peanut protein allergen mentioned above wherein the modified peanut protein allergen retains the ability to initiate a Th1-type response; (9) a composition comprising said modified peanut protein allergen as set forth in (1) and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18 and IFNγ; (10) the modified peanut protein allergen mentioned above is made in a transgenic plant or animal; (11) the modified peanut protein allergen mentioned above is expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells; (12) the modified peanut protein allergen mentioned above expressed in a recombinant host selected from the group consisting of bacteria, yeast,

fungi, and insect cells; (13) the modified peanut protein allergen mentioned above wherein the unmodified peanut allergen is obtained from legumes; (14) the modified peanut protein allergen mentioned above made by the process of identifying at least one IgE epitope in an unmodified peanut protein allergen; preparing at least one modified protein allergen whose amino acid sequence is identical to that of an unmodified peanut protein allergen except that at least one amino acid has been modified in at least one IgE epitope; screening for IgE binding to the at least one modified protein allergens by contacting the at least one modified protein allergens with serum IgE taken from at least one individual that is allergic to the unmodified peanut protein allergen, and selecting a modified protein allergen with decreased binding to IgE as compared to the unmodified peanut protein allergen and (15) the modified peanut allergen mentioned above wherein the unmodified peanut allergen is selected from the group consisting of Ara h1, Ara h2 and Ara h3 for immunotherapy, **does not** reasonably provide enablement for (1) *all* "modified protein allergen" whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen as set forth in claims 37-46, 48-51, and 53 wherein the unmodified protein allergen is from any legumes, any milks, any grains, any eggs, any fish, any crustacean, any mollusks, any insects, any molds, any dust, any grasses, any tress, any weeds, any mammals, and any natural latexes, (2) *all* modified protein allergen wherein the at least one IgE epitope contains 1-6, 1-5, 1-4, 1-3, 1-2 or any 1 amino acid residue that is modified as set forth in claims 65-70; (3) *any* composition comprising all "modified protein allergen" and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ and any immune stimulatory sequences as set forth in claim 47, (4) *all* "modified food allergen" from any unmodified food allergen such as any legumes other than peanuts, any milks, any eggs, any fish, any crustaceans, any mollusks, any wheat, any barley, cow milk, egg, codfish, hazel not, soybean, and shrimp as set forth in claim 60-62, (5) *all* "modified food allergen" wherein the at least one IgE epitope contains any 1-6, 1-5, 1-4, 1-3, 1-2 or any 1 amino acid residue that is modified as set forth in claims 65-70; (6) *all* "modified peanut allergen" as set forth in claim 63 (7) *all* "modified peanut allergen" wherein the at least one IgE epitope contains 1-6, 1-5, 1-4, 1-3, 1-2 or any 1 amino acid residue that is modified as set forth in claims 65-70, and (8) any modified protein allergen, any modified food allergen, and any modified peanut allergen wherein binding by serum IgE to the at least one epitope is reduced for the modified allergen to less than about 1% of that observed to the unmodified allergen for use in immunotherapy, vaccine, and to genetically engineer organisms such as plants and animals to produce proteins with less likelihood of eliciting an IgE response.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three peanut allergens Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) as depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification discloses only three modified peanut allergens Ara h1, Ara h2 and Ara h3. The modified peanut allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M (page 24). The specification discloses a second modified peanut allergen Ara h2 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and a third modified peanut allergen Ara h3 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy. The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a *reduced* IgE binding. In contrast, substituting alanine for arginine of Ara h1 leads to an *increased* IgE binding

(See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type (unmodified peanut allergen) but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

Besides the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 mentioned above, there is insufficient guidance without the amino acid sequence as how to make all modified protein allergens, all modified food allergens from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp whose amino acid sequence is "substantially" identical to any unmodified protein allergen or any food allergen. Second, there is a lack of guidance as to which amino acid within which IgE epitope of the full length sequence to be modified such as substitution, deletion or addition and whether the resultant modified protein allergen reduces IgE binding, retains the ability to bind IgG and/or initiate a Th1-type response. Third, the specification does not define the term "substantially". A modified protein allergen could be 50% identical to unmodified protein would still be "substantially identical" to that of unmodified protein allergen. Fourth, the term "at least one" has no upper limit as to how many amino acid residues could be modified by substitution, deletion or addition, much less which amino acid to be substituted in which IgE epitope (since allergens has more than one IgE epitomes) within the full length protein allergen. Fifth, given the unlimited number of modified protein allergen and modified food allergens, there is insufficient working examples demonstrating that all modified protein allergens, all modified food allergens that after substitution, deletion, or addition would retain the ability to activate T cells, bind IgG, initiate a Th-1 type response, and/or reduce binding to IgE, in turn, useful for treating any allergy. Sixth, even if the sequence of protein and food allergen are known as asserted by applicant, the specification fails to provide guidance as to which amino acid is critical to IgE binding within the at least one IgE epitope in reference to the full length polypeptide in all protein allergen and all food allergen such as food allergens from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, weeds, trees, mammals, and natural latexes. Even if the IgE epitope has been identified in some of the food

allergen, there is no consensus that modifying any 1-6, 1-5, 1-4, 1-3, 1-2 or any amino acid within the IgE epitope would lead to decrease IgE binding, in turn, would be useful for treating allergy or to genetically engineer organisms such as plants and animals to produce proteins with less likelihood of eliciting an IgE response. There is no recognition in the art that sequence identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Fasler *et al.* (of record, PTO 892) teach modified protein allergen derived from house dust mite Der p1 that has been modified by amino acid substitutions at positions 173, 175, 176, 180 and 181 for alanine or glycine. However, these modified protein allergen fail to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al* further teach that substituting a neutral amino acid residue such as Asn at position 173 for either a basic residue such as Lysine, or a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al.* (of record, PTO 1449) teach a modified food allergen from peanut such as Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine. The modified peanut allergen reduces IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* (of record, PTO 1449) teach a modified food allergen from peanut such as Ara h2 by amino acid substitution with alanine at position 67, 68 or 69. The modified peanut allergen having alanine substitution at position 67, 68 and 69 significantly reduced IgE binding. In contrast, substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding.

Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al* (of record, PTO 892) teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al* (of record, PTO 892) teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular). Until the amino acids that are critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding or within the full length polypeptide in all protein allergen, all food allergen and all peanut allergens other than Ara h1, 2, 3 have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described, it would require an undue amount of experimentation for one of skill in the art to arrive at the scope of the claimed invention. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment. Since the modified protein allergen mentioned above is not enabled, it follows that the composition comprising said modified protein allergen and adjuvant is not enabled. It also follows that any undisclosed modified protein allergen made in a transgenic plant or animal or recombinant host are not enabled.

Even if the specific peanut food allergen is recited in claim 64, only the specific amino acid substitutions within the full length of SEQ ID NO: 1 and 2 such as the ones disclosed on page 24, lines 16-24 or the ones shown in page 24, Table 4-6 have reduced IgE binding less than 1% of that observed to the unmodified peanut allergens. Given the indefinite number of undisclosed modified protein allergen, modified food allergen, it is unpredictable which undisclosed modified protein allergen and food allergen would reduce IgE binding, activate T cells and/or bind IgG, in turn, would be useful for immunotherapy.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the

specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112 Written Description

Claims 37-51, 53, and 60-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *all* "modified protein allergen" whose amino acid sequence is "substantially" identical to that of *any* unmodified protein allergen as set forth in claims 37-46, 48-51, and 53 wherein the unmodified protein allergen is from any legumes, any milks, any grains, any eggs, any fish, any crustacean, any mollusks, any insects, any molds, any dust, any grasses, any tress, any weeds, any mammals, and any natural latexes, (2) *all* modified protein allergen wherein the at least one IgE epitope contains 1-6, 1-5, 1-4, 1-3, 1-2 or any 1 amino acid residue that is modified as set forth in claims 65-70; (3) *any* composition comprising all "modified protein allergen" and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ and any immune stimulatory sequences as set forth in claim 47, (4) *all* "modified food allergen" from any unmodified food allergen such as any legumes other than peanuts, any milks, any eggs, any fish, any crustaceans, any mollusks, any wheat, any barley, cow milk, egg, codfish, hazel not, soybean, and shrimp as set forth in claim 60-62, (5) *all* "modified food allergen" wherein the at least one IgE epitope contains any 1-6, 1-5, 1-4, 1-3, 1-2 or any 1 amino acid residue that is modified as set forth in claims 65-70; (6) *all* "modified peanut allergen" as set forth in claim 63 (7) *all* "modified peanut allergen" wherein the at least one IgE epitope contains 1-6, 1-5, 1-4, 1-3, 1-2 or any 1 amino acid residue that is modified as set forth in claims 65-70, and (8) any modified protein allergen, any modified food allergen, and any modified peanut allergen wherein binding by serum IgE to the at least one epitope is reduced for the modified allergen to less than about 1% of that observed to the unmodified allergen.

The specification discloses only three peanut allergens Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) as depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification discloses only three modified peanut allergens Ara h1, Ara

h2 and Ara h3. The modified peanut allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M (page 24). The specification discloses a second modified peanut allergen Ara h2 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and a third modified peanut allergen Ara h3 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy. The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a *reduced* IgE binding. In contrast, substituting alanine for arginine of Ara h1 leads to an *increased* IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type (unmodified peanut allergen) but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

With the exception of the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 mentioned above, there is insufficient written description about the structure without the amino acid sequence of *all* modified protein allergen, *all* modified food allergen and *all* modified peanut allergen other than Ara h1, 2 and 3. The specification does not provide a description of structural features that are common to IgE epitopes other than the peanut allergens specifically exemplified. In fact, the specification discloses that IgE epitopes of peanut allergens shared no common amino acid sequence motif (See Table 4-6 on page 26-27). The specification does not provide a

description of polypeptide of all modified protein allergen, and polypeptide of all modified food allergen other than the peanut allergens specifically exemplified. Neither the specification's description of exemplary modified IgE epitopes from only three peanut allergens nor its general description of how those skilled in the art could find other IgE epitopes to make other modified protein allergen, modified food allergen and modified peanut allergen (claim 63) is adequately to described the genus defined by claims 37, 60 and 63. With regard to the term "substantially identical", the specification does not defined the term "substantially identical". A modified protein allergen could be 50% identical to unmodified protein would still be "substantially identical" to that of unmodified protein allergen. Further, the term "at least one" has no upper limit as to how many amino acid residues could be modified by substitution, deletion or addition, much less which amino acid to be substituted for which amino acid within which IgE epitope (since allergens has more than one IgE epitomes) and within the full length of all protein allergens, all food allergens and all peanut allergens.

Until the amino acid critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding or within the full length polypeptide in all modified protein allergen, all modified food allergen and all peanut allergens other than Ara h1, 2, 3 have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described, the modified protein allergen, and the modified food allergen obtained from a source selected from the group consisting of legumes other than peanut, milks, grains, eggs, fish, crustaceans and mollusks, wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp are not adequately described. Since the structure of the modified protein allergen (claims 37), the structure of modified food allergen (claim 60) and the structure of modified peanut allergen other than Ara h1, 2, and 3 (claim 63) have not been adequately described, it follows that the modified protein allergen that retains the ability to activate T cells (claim 43), or binds IgG (claim 44), or retains the ability to initiate a Th1 type response (claim 45) are not adequately described. It also follows that the composition comprising the undisclosed modified protein allergen and the adjuvant such as the ones recited in claim 47 is not adequately described. Since the structure such as the amino acid sequence of all modified food allergen is not adequately describe, it follows that the modified protein expressed in a recombinant host such as the ones recited in claims 49-50 are not adequately described.

Even if the modified peanut allergen is limited to Ara h1, Ara h2 and Ara h3 (claim 64), there is insufficient written description about the structure of said modified allergens without reciting the amino acid sequence in the claim.

The specification discloses only three modified food allergens from only peanut. Given the lack of a written description of *any* additional representative species of modified protein, modified food allergen from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, codfish, hazel nut soybean and shrimp, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 112 New matter

Claims 65-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

Claims 65-69 as written represent a departure from the specification and the claims as originally filed.

The "modified protein allergen or modified food allergen wherein at least one IgE contains 1-6 amino acid residues" in claim 65 has no support in the specification and the claims as originally filed.

The "modified protein allergen or modified food allergen wherein at least one IgE contains 1-5 amino acid residues" in claim 66 has no support in the specification and the claims as originally filed.

The "modified protein allergen or modified food allergen wherein at least one IgE contains 1-4 amino acid residues" in claim 67 has no support in the specification and the claims as originally filed.

The "modified protein allergen or modified food allergen wherein at least one IgE contains 1-3 amino acid residues" in claim 68 has no support in the specification and the claims as originally filed.

The "modified protein allergen or modified food allergen wherein at least one IgE contains 1-2 amino acid residues" in claim 69 has no support in the specification and the claims as originally filed. Appellant has not pointed out the support for said "1-6, 1-5, 1-4, 1-3 and 1-2 amino acid residues" in any modified protein allergen, and any modified food allergen other than the specific peanut allergen shown in Table 4-6 of the specification. Even if the claims are limited to modified peanut allergens, the specific "1-6", "1-5", "1-4", "1-3" and "1-2" have no support in the specification as filed.

Claim Rejections - 35 USC § 112 Second paragraph

Claims 37, 60 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "substantially identical" in claims 37, 60 and 63 is ambiguous and one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention because the specification does not define the term "substantially". The modified protein could be 50% identical to the unmodified protein would still meet the claimed limitation. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

Claim Rejections - 35 USC § 102(b)

Claims 37-39, 41-46, 48-51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,547,669 (Aug 1996, PTO 892).

The '669 patent teaches a modified protein allergen such as FEL DI from cat which is a mammal, whose amino acid sequence is substantially identical to that of an unmodified protein allergen and that the modified protein has reduced IgE binding (See column 3, lines 36-45, in particular). The reference modified protein allergen (recombitope peptide) is a portion of the unmodified protein allergen from cat produced by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). The reference modified protein allergen is expressed recombinantly in

host cell such as bacteria (E coli), and the reference modified protein allergen stimulates T cell activity such as T cell proliferation better than unmodified protein allergen (See column 24, lines 8-67, bridging column 25, lines 1-32, in particular), initiates delayed type sensitivity which is Th-1 response (See column 26, lines 60-62, in particular) and reduces IgE binding (See column 22, lines 44, column 23, lines 59-61, in particular). Claims 48-49 are included in this rejection because a product is a product, irrespective of how it is made. The recitation of a process limitation in claim 48-49 is not seen as further limiting the claimed product, since multiple processes can make equivalent products. The reference modified protein allergen inherently has the ability to bind IgG since the reference modified protein is modified the same way as that of the specification on page 24 such as substituting neutral amino acid alanine (See column 15, lines 1-5, 15-17) or hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62 of '669, in particular). Since the Patent Office does not have the facilities for examining and comparing the modified protein allergen of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the antibodies of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The '669 patent further teaches a method for designing recombitope peptides of any allergen where the protein antigen to which the individual is senstive has unknown or ill-defined epitope (See abstract, in particular) and the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular). Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 102(a)

The filing date of the instant claims 37, 60-61 and 65-71, is deemed to be the filing date of instant application while the filing date of instant claims 63-64 is deemed to be the filing date of the priority application 60/073,283, 60/074,633, 60/074,624, 60/074,590 that all filed Feb 13, 1998 because (1) the 08/717,933 application filed Sept 23, 1996 discloses only the specific modified peanut allergen Ara h1, and Ara h2 (page 194), monoclonal antibody specific to a selected peanut allergen, hybridoma and immunoassay to be used for determining the concentration of a specific allergen (Ara h I) (See summery of invention, pages 6-12, claims of 08/717,933, in particular). (2) The USSN 08/717,933 does not support the claimed limitations of any modified protein allergen (claims 37-51), any modified food allergen (claims 60-62), any modified peanut allergen other than Ara h1 and 2 (claim 63), the modified Ara h3 allergen (claim

64), the "1-6 amino acid residues" of any modified protein allergen or any modified food allergen (claim 64), the "1-5 amino acid residues" of any modified protein allergen or any modified food allergen (claim 66), 1-4 amino acid residues" of any modified protein allergen or any modified food allergen (claim 67), 1-3 amino acid residues" of any modified protein allergen or any modified food allergen (claim 68), the "1-2 amino acid residues" of any modified protein allergen or any modified food allergen (claim 69). (3) the priority applications 60/073,283, 60/074,633, 60/074,624, 60/074,590 all filed Feb 13, 1998 disclose only modified peanut allergen Ara h1, Ara h2 and Ara h3. Applicants are reminded that such priority for the instant limitations requires a written description and enablement under 35 U.S.C. § 112, first paragraph. Therefore, The filing date of the instant claims 37, 60-61 and 65-71, is deemed to be the filing date of instant application while the filing date of instant claims 63-64 is deemed to be the filing date of Feb 13, 1998.

Claims 37, 60-61 and 63-71 are rejected under 35 U.S.C. 102(a) as being anticipated by Burks *et al* (Eur. J. Biochem. 245: 334-339; April 1997, PTO 1449; see entire document).

Burks *et al* teach a modified protein allergen such peanut (food) allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified food allergens such as peanut Ara h1 except that one amino acid has been modified in one of the IgE epitope so that IgE binding to the reference modified food allergen is reduced as compared with IgE binding to the unmodified peanut allergen, and the reference IgE epitope is recognized by 15 individuals who is allergic to the unmodified peanut allergen (See entire document, Materials and Methods, Fig 6, in particular). The reference modified protein allergen is based on a protein obtained from legumes, which peanut is part of the family. The reference modified protein allergen whose immunodominant IgE epitope of unmodified Ara h1 protein or portion thereof can be mutated to non-IgE binding epitopes by a single amino acid changes (See Fig. 6-7, in particular). The modified reference allergen is mutated in the center of one or more IgE binding epitopes by substituting a hydrophobic amino acid (Ala) in the center of one or more of the IgE binding sites with a neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, in particular). The modified allergen is made by the process of identifying one or more IgE binding sites in an allergen, mutating one or more amino acid in an IgE binding site, screening for IgE binding to the mutated allergen and selecting the modified allergens with the least binding to IgE (See Fig 2 and 3; page 247; page 246 for IgE-binding assay, in particular). The reference further

teaches there are at least 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and the modified allergen is a portion of a protein (See Figs 1-3, Fig 6, page 339, column 1, in particular). Burks *et al* teach it is possible to mutate the Ara h1 allergen to a protein so that it no longer binds IgE and this could be used to replace its allergenic homologue in the peanut genome to develop a hypoallergenic peanut and for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Claims 65-69 are included in this rejection because the reference teaches there are at least 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and the modified allergen is a portion of a protein (See Figs 1-3, Fig 6, page 339, column 1, in particular) and mutates at least one amino acid in the IgE in an IgE binding site (See Fig 2 and 3; page 247; page 246 for IgE-binding assay, in particular) to develop a hypoallergenic peanut for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). The reference modified-allergen has reduced IgE binding to less than about 1% of that observed to the unmodified allergen (See Fig 4 and 5, in particular). Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103(a)

1. **Claims 37 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) in view of Hoyne *et al* (of record, Immunology and Cell Biology 74: 180-186, 1996, PTO 892).**

The teachings of the '669 patent have been discussed supra.

The claimed invention in claim 47 differs from the teachings of the reference only in that a composition comprising the modified allergen and an adjuvant such as IL-12, and IFNγ.

Hoyne *et al.* teach patients receiving the PLA-2 specific peptides from bee venom demonstrated a decrease in allergen specific IgE and a corresponding rise in IgG levels; most patients reported a significant improvement in clinical symptoms (See page 183, column 1, paragraph 2, in particular). Hoyne *et al.* further teach peptide-mediated regulation of allergic immune response and a successful desensitization using peptide-mediated immunotherapy is accompanied by a decrease Th2-type cytokine with a concomitant increase in IFNγ production (See page 180, column 2, in particular). The reference further teaches that the key to successful immunotherapy may dependent on reprogramming the immune response by co-administering

modified allergen peptide in the presence of adjuvant such as IL-12 or IFNγ (See page 183, column 2, paragraph 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate or combine any modified allergen as taught by the '669 patent with the IL-12 or IFNγ as taught by Hoynes et al because the key to a successful peptide-based immunotherapy depends on reprogramming the immune response by co-administering allergen peptide in the presence of IL-12 or IFNγ since IL-12 or IFNγ would down-regulate ongoing Th2 responses in vivo by suppressing IgE production as taught by Hoyne et al (See page 183, column 2, in particular).

2. **Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) in view of Burks *et al* (of record, J Allergy Clin Immunol 6-93(4): 743-50; 1994 PTO 1449).**

The teachings of the '669 patent have been discussed supra.

The claimed invention in claim 37 differs from the teachings of the reference only in that the modified protein allergen is peanut protein of Ara h1 and Ara h2.

Burks *et al* teach a major allergen of peanuts such as Ara h1 and the IgE binding specificity of Ara h1 antibodies is determined by competition ELISA using pooled peanut-specific IgE from patients allergic to the natural protein peanut allergen (See page 746, Table II, in particular). Burks et al further teach that the allergen is purified by affinity column chromatography and the Ara I allergen has a molecular weight of 63.5 kd and an isoelectric point of 4.55 while the second allergen such as Ara II has a molecule weight of 17 kd and an isoelectric point of 5.2 (See Abstract, page 749, column 1, first full paragraph, in particular). The reference further teaches that peanuts are considered one of the most allergenic food (See page 743, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cat allergen as taught by the '669 patent for the peanut allergen such as Ara h1 or Ara h2 as taught by Burks et al and modifying any one amino acid in the unmodified peanut allergen by alanine substitution as taught by '669 patent such that the modified peanut is no longer binds IgE as taught by the '669 patent for desensitization immune therapy. The amino acid that has been modified is obviously within the IgE epitope since the modified peanut allergen is now longer binds IgE. From the combined teachings of the

references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify peanut allergen Ara h1 and Ara h2 because Burks *et al* teach peanuts are considered one of the most allergenic food (See page 743, column 1, in particular), the IgE binding epitope can be easily determined by IgE inhibition experiments using pooled peanut-specific IgE from patients allergic to the natural protein peanut allergen (See page 746, Table II, in particular) or monoclonal antibodies that bind specifically to Ara h 1 (See page 749, col. 1, Discussion, in particular). The '699 patent teaches that modified protein allergen with reduced IgE binding is useful for desensitize the individual to said protein allergen (See column 3, lines 34-36, in particular).

3. **Claims 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) or Burks *et al* (Eur. J. Biochem. 245: 334-339, April 1997; PTO 1449) each in view of US Pat No. 5,449,669 (Sept 1995, PTO 892).**

The teachings of the 5,547,669 patent and Burks *et al* (1997) have been discussed supra.

The invention in claim 61 differs from the teachings of the references only in that the unmodified protein allergen is obtained from crustacean.

The claimed invention in claim 62 differs from the teachings of the references only in that the unmodified protein allergen is obtained from shrimp.

The 5,449,669 patent teaches allergen obtained from unmodified food allergen such as shrimp, which is a member of crustacean family and IgE binding epitopes in shrimp (See abstract, in particular). The reference IgE epitopes are useful in diagnosis and/or treatment of allergies.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made substitute the cat allergen as taught by the 5,547,669 patent or the peanut allergen as taught by Burks et al for the food allergen such as shrimp as taught by the 5,449,669 patent and modifying at least one amino acid within the IgE binding epitopes of shrimp as taught by the 5,449,669 patent using the method as taught by the 5,547,669 patent or Burks *et al* for a modified food allergen that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified protein allergen as taught by the 5,547,669 patent and Burks et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the 5,449,669 patent teaches IgE epitopes from shrimp are useful in diagnosis and/or treatment of allergies. The 5,547,669 patent the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular). Burks *et al* teach that it is possible to mutate any allergen to a protein so that it no longer binds IgE for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph).

(11) Response to Argument

Claim Rejections - 35 USC § 112 enablement

At pages 5-8 of the Brief, Appellant submits that claims of Group A, B and C are of different scope since they relate to modified protein allergens, modified food allergens and modified peanut allergens, respectively. The Examiner has explicitly conceded that the subject matter of Groups B and C is enabled and therefore these groups will stand or fall together. Appellant submits that the claims of Group A are also enabled and that these claims stand or fall together because in light of the teachings of the specification, no undue experimentation is required to obtain modified protein allergens other than modified food and peanut allergens and Appellants begins by summarizes the Wands factors.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. In contrast to Appellant' argument that the Examiner has explicitly conceded that the subject matter of Groups B and C as being enabled, the examiner states that only the modified *peanut* protein allergen selected from the group consisting of Ara h1, Ara h2 and Ara h3 such as the ones shown in page 24, Table 4-6 (pages 26-27) are enabled. It is noted that the scope of claims 37-51, 53 and 65-71 (Group A) encompasses any modified protein allergen. The scope of claims 60-62 and 65-71 (Group B) encompasses any modified food allergen, such as modified allergens from any legumes, any milks, any grains, any eggs, any fish, any crustaceans, any mollusks, any wheat, any barley, any cow milk, any codfish, any hazel nut, and shrimp. The scope of claims 63-64 and 65-71 (Group C) encompasses any modified peanut allergens.

The specification discloses only three peanut allergens Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) as depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively

(See page 26-27). The specification discloses only three modified peanut allergens Ara h1, Ara h2 and Ara h3. The modified peanut allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M (page 24). The specification discloses a second modified peanut allergen Ara h2 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and a third modified peanut allergen Ara h3 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy. The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a *reduced* IgE binding. In contrast, substituting alanine for arginine of Ara h1 leads to an *increased* IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type (unmodified peanut allergen) but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

Besides the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 mentioned above, there is insufficient guidance without the amino acid sequence as how to make all modified protein allergens, all modified food allergens from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp whose amino acid sequence is "substantially" identical to any unmodified protein allergen or any food allergen. Second, there is a lack of guidance as to which amino acid

within which IgE epitope of the full length sequence to be modified such as substitution, deletion or addition and whether the resultant modified protein allergen reduces IgE binding, retains the ability to bind IgG and/or initiate a Th1-type response. Third, the specification does not define the term "substantially". A modified protein allergen could be 50% identical to unmodified protein would still be "substantially identical" to that of unmodified protein allergen. Fourth, the term "at least one" has no upper limit as to how many amino acid residues could be modified by substitution, deletion or addition, much less which amino acid to be substituted in which IgE epitope (since allergens has more than one IgE epitomes) within the full length protein allergen. Fifth, given the unlimited number of modified protein allergen and modified food allergens, there is insufficient working examples demonstrating that all modified protein allergens, all modified food allergens that after substitution, deletion, or addition would retain the ability to activate T cells, bind IgG, initiate a Th-1 type response, and/or reduce binding to IgE, in turn, useful for treating any allergy. Sixth, even if the sequence of protein and food allergen are known as asserted by applicant, the specification fails to provide guidance as to which amino acid is critical to IgE binding within the at least one IgE epitope in reference to the full length polypeptide in all protein allergen and all food allergen such as food allergens from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, weeds, trees, mammals, and natural latexes. Even if the IgE epitope has been identified in some of the food allergen, there is no consensus that modifying any 1-6, 1-5, 1-4, 1-3, 1-2 or any amino acid within the IgE epitope would lead to decrease IgE binding, in turn, would be useful for treating allergy or to genetically engineer organisms such as plants and animals to produce proteins with less likelihood of eliciting an IgE response. There is no recognition in the art that sequence identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Fasler *et al.* (of record, PTO 892) teach modified protein allergen derived from house dust mite Der p1 that has been modified by amino acid substitutions at positions 173, 175, 176, 180 and 181 for alanine or glycine. However, these modified protein allergen fail to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al* further teach that substituting a neutral amino acid residue such as Asn at position 173 for either a basic residue such as Lysine, or a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180

and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al.* (of record, PTO 1449) teach a modified food allergen from peanut such as Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine. The modified peanut allergen reduces IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* (of record, PTO 1449) teach a modified food allergen from peanut such as Ara h2 by amino acid substitution with alanine at position 67, 68 or 69. The modified peanut allergen having alanine substitution at position 67, 68 and 69 significantly reduced IgE binding. In contrast, substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al* (of record, PTO 892) teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al* (of record, PTO 892) teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular). Until the amino acids that are critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding or within the full length polypeptide in all protein allergen, all food allergen and all peanut allergens other than Ara h1, 2, 3 have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described, it would require an undue amount of experimentation for one of skill in the art to arrive at the scope of the claimed invention. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not

a license to experiment. Since the modified protein allergen mentioned above is not enabled, it follows that the composition comprising said modified protein allergen and adjuvant is not enabled. It also follows that any undisclosed modified protein allergen made in a transgenic plant or animal or recombinant host are not enabled.

Even if the specific peanut food allergen is recited in claim 64, only the specific amino acid substitutions within the full length of SEQ ID NO: 1 and 2 such as the ones disclosed on page 24, lines 16-24 or the ones shown in page 24, Table 4-6 have reduced IgE binding less than 1% of that observed to the unmodified peanut allergens. Given the indefinite number of undisclosed modified protein allergen, modified food allergen, it is unpredictable which undisclosed modified protein allergen and food allergen would reduce IgE binding, activate T cells and/or bind IgG, in turn, would be useful for immunotherapy.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

At page 9 of the Brief, appellant argues that the present application clearly states that its teachings are also applicable to other non-peanut allergens (e.g., see pages 7-9). The present application clearly sets forth all the steps necessary to identify and prepare suitable modified protein allergens that fall within the scope of the broadest claims, namely using patient sera to identify IgE binding epitopes; modifying a protein allergen sequence to alter identified IgE binding epitopes; and screening modified protein allergens to identify those with reduced binding. It is further undisputed that the sequences of numerous non-peanut protein allergens were known at the time of filing (a number of these are highlighted in the specification, e.g., see pages 7-9; others were known as evidenced by the numerous references and accession numbers that are provided in the Official list of allergens," maintained by the RJIS Allergen Nomenclature Subcommittee and provided as Attachment II). For some of these protein allergens IgE binding sites were also already known (e.g., see page 8, lines 4-13). In addition, methods of identifying and modifying IgE binding sites were known and further described in the specification (e.g., see

Examples 1 and 2). Those skilled in the art were also familiar with the methods that were used by the inventors to screen modified protein allergens for IgG and IgE binding and T-cell stimulation (e.g., see Examples 3 and 4). At the time the application was filed, the starting materials necessary to obtain modified protein allergens were therefore available and the techniques for performing the necessary steps were well known and routine.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. Appellant appears to argue for a method of making modified allergen. It is noted that none of the instant claims are drawn to a method of making modified protein allergen. The scope of claims 37-51, 53 and 65-71 (Group A) encompasses any modified protein allergen. The scope of claims 60-62 and 65-71 (Group B) encompasses any modified food allergen, such as modified allergens from legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, codfish, hazel nut, and shrimp. The scope of claims 63-64 and 65-71 (Group C) encompasses any modified peanut allergens. The specification on page 7-9 merely alludes to protein of the food allergens from peanuts, milk, grains such as Barley, soybeans, eggs, fish, crustaceans, and mollusks, codfish, hazel nut, and fish. The laundry list of protein allergen such as the ones mentioned above and the ones attached in Appendix II do not provide the structure of all modified protein allergen, all modified food allergen and the modified peanut allergens wherein at least one amino acid has been modified in at least one or all IgE epitopes so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen without the amino acid sequence. Without the amino acid structure of all the modified protein allergen and modified food allergen, one skill cannot make, much less use the modified protein allergen or modified food allergen. The specification (page 7) discloses "The first step in making the modified allergen is to identify IgE binding sites and/or immunodominant IgE binding sites. The second step is to mutate one or more of the 1gE binding sites, preferably including at a minimum one of the immunodominant sites, or to react the allergen with a compound that selectively blocks binding to one or more of the IgE binding sites. The third step is to make sufficient amounts of the modified allergen for administration to persons or animals in need of tolerance to the allergen, where the modified allergen is administered in a dosage and for a time to induce tolerance, or for diagnostic purposes. The modified allergen can be administered by injection, or in some cases, by ingestion or inhalation." These generic steps merely extend an invitation to one skill in the art for further experimentation to arrive at the claimed modified protein allergen and modified food allergen.

In response to Appellant's argument that the sequences of numerous non-peanut protein allergens were known at the time of filing (a number of these are highlighted in the specification, e.g., see pages 7-9; others were known as evidenced by the numerous references and accession numbers that are provided in the Official list of allergens," maintained by the RJIS Allergen Nomenclature Subcommittee and provided as Attachment II), this is merely an invitation to the artisan to use the current invention and the available sequences of non-peanut protein allergens as a starting point for further experimentation to arrive at other modified protein allergen or modified food allergen. Until the amino acid critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding or within the full length polypeptide in all protein allergen, all food allergen and all peanut allergens other than Ara h1, 2, and 3 have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described, it would require an undue amount of experimentation for one of skill in the art to arrive at the scope of the claimed invention. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

At page 10 of the Brief, appellant argues that there is no particular magic in the sequence of the peanut or food allergens that makes these protein allergens more susceptible to the inventive methods; the inventive principles, as discussed in the present application, apply to other protein allergens as well. In fact, quite the opposite might be expected. Peanut proteins are highly allergenic and, like many other food allergens (as distinguished, for example from most pollens and danders) present a significant risk of anaphylaxis to those allergic to them. The inventive demonstration that such anaphylactic proteins can be modified so that IgE binding is reduced as compared with the unmodified protein provides a strong teaching to those of ordinary skill in the art that other modified protein allergens with reduced 1gE binding can also be made.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. In contrast to appellant's assertion that other nucleotide molecule encoding modified protein allergens with reduced IgE binding can also be made without guidance, Fasler *et al* further teach that substituting a neutral amino acid residue such as Asn at position 173 for either a basic residue such as Lysine, or a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid

positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al.* (of record, PTO 1449) teach a modified food allergen from peanut such as Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine. The modified peanut allergen reduces IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* (of record, PTO 1449) teach a modified food allergen from peanut such as Ara h2 by amino acid substitution with alanine at position 67, 68 or 69. The modified peanut allergen having alanine substitution at position 67, 68 and 69 significantly reduced IgE binding. In contrast, substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). In fact, the specification on page 24 discloses that substituting amino acids at position 144, 145, 147 and 148 of SEQ ID NO: 12 (Ara h1) for Met results in less than 1% of peanut specific IgE binding (decrease) to these peptides. However, the substitution of an alanine (Ala) for Arginine at position 152 of Ara h1 shown in SEQ ID NO: 2 resulted in *increased* IgE binding. Thus the effects of these changes to the polypeptide of any allergen, the corresponding polynucleotide encoding the modified allergen are largely unpredictable.

At pages 10-11 of the Brief, appellant argues that others have prepared modified protein allergens according to the teachings of the application without undue experimentation. Appellant cites various post filing date references, i.e. Schramm et al teach "allergen engineering: variants of the Timothy grass pollen allergen Phl p5b with reduced IgE-binding capacity but conserved T cell reactivity" J. Immunol 162: 2406-2414, 1999. Robotham et al for teaching linear IgE epitope mapping of the English walnut (*Juglans regia*) major food allergen, Jug r1", J. Allergy Clin.

Immuol. 109: 143-149, 2002. Astwood et al., "identification and characterization of IgE binding epitopes of patatin, a major food allergen of potato", J Allerp Clin. Immunol. 105:5184 (Abstract 555), 2000. Helm et al., "Mutational analysis of the IgE-binding epitopes of P34/Gly m Bd 30K", J Allergy Clin. Immunol. 105: 378-384, 2000. Ayuso et al., "identification and mutational analysis of major epitopes of the shrimp allergen Pen a 1 Tropomyosin l", (J Allergy Clin. Immunol. 105:S140 (Abstract 423), 2000 and Lehrer et al., "current understanding of food allergens", Ann. NY Acad Sci. 964:69-85, 2002 to show that the inventive principles, once demonstrated may be readily applied to other protein allergens, including food allergens.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The pending claims 37-51, 53 and 65-71 (Group A) encompass any modified protein allergen. The scope of claims 60-62 and 65-71 (Group B) encompasses any modified food allergen, such as modified allergens from legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, codfish, hazel nut, and shrimp. The scope of claims 63-64 and 65-71 (Group C) encompasses any modified peanut allergens. It is noted that the pending claims are not drawn to a method of making modified peanut allergen.

With respect to the Schramm et al reference, Schramm et al teach protein allergen contains continuous and discontinuous IgE epitopes spreading over the entire molecule and recognized individually by different patients (see page 2412, col. 2, page 2413, col. 2, in particular) and finding the exact location of such discontinuous IgE epitopes by fragmentation of the allergen is NOT possible (See page 2409, col. 1, in particular). Schramm et al teach various amino acid substitution at the N terminal of IgE epitope from D at position 49 to L and K50 to A (PM1) and amino acid substitution from A 13 to C (PM3) in Timothy Grass Pollen fail to reduce IgE binding (See page 2409, col. 2 last paragraph, in particular) while deletion mutants DM2 (and DM4 (A220 to T) reduce IgE binding. Schramm further states that it is expected that exchange of one or few amino acids does not lead to complete loss of IgE reactivity (IgE binding) (See page 2412, col. 2, in particular). Thus the effects of these changes to the polypeptide of any protein allergen are largely unpredictable.

With respect to the Robotham et al reference, Robotham et al merely describes the mapping of a linear IgE epitope of English walnuts. Robotham et al do not teach nucleotide molecule encoding modified English walnut nor nucleotide molecule encoding any modified food allergen as required by the claims. Robotham et al teach allergen specific IgE binding epitopes could be linear or conformational (See page 147, col. 2, last paragraph, in particular). Robotham

et al further teach, "to date, no common structural character of liner IgE epitopes has been identified" (See page 148, col. 1, first paragraph, in particular). The identification of only one linear IgE epitope to English walnut is unique in that all previously analyzed allergens contain multiple linear IgE epitopes as well as conformational epitopes and that conformational epitopes are important and key in IgE binding (See page 148, col. 1, first paragraph, in particular). More importantly, the mutational analysis of Jug r1 IgE binding epitope as shown in Table I on page 145 of the reference shows that amino acid substitution from Q to A at position 1 increases IgE binding whereas amino acid substitution from E to A at position leads to decrease IgE binding. Again, there is no obvious position within each peptide, the corresponding polynucleotide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding. Thus the effects of these changes to the polypeptide of any food allergen are largely unpredictable.

With respect to the Beezhold et al reference (J Allergy Clin Immunol 107: 1069-1076, 2001), Beezhold et al teach mutational analysis of IgE epitopes in the latex allergen Hev b5 by alanine substitution (See entire document, page 1072, col. 2, Table 1, in particular). Beezhold et al teach functional changes that reduce IgE binding need to be determine to produce modified allergens for immunotherapy and mutation of single epitopes had little influence on IgE binding (See page 1075, col. 1, par.2-3, in particular). Beezhold et al teach that human IgE response is polyclonal and heterogeneous and multiple changes in protein allergens appear necessary to reduce the potential for recognition (IgE binding) of the hypoallergenic mutant (page 1075, col. 2, in particular). A change of minimal three immunodominant epitopes is required to cause a 100-fold reduction in IgE binding and a change in 8 epitopes are need to maximize the reduction of IgE binding (See abstract, in particular). Beezhold et al concludes "we were unable to significantly reduce IgE binding to the clones until both epitopes 5.7 (aa 86-98) and 5.9 (aa 124-132) were altered (See page 1075, col. 2, Table 1, in particular). Thus the effects of these changes to the polypeptide of any protein allergen are largely unpredictable.

With respect to the Swoboda et al reference (Eur J. Immunol 32: 270-280, 2002), Swoboda et al teach modified ryegrass pollen allergen Lol p5 by single or multiple amino acid substitutions (See entire document, page 272, col. 2, in particular). Swoboda et al teach a single amino acid exchange K57 to A resulted in reduction in IgE binding in four out of the six sera from patients with allergy to rye grass. In contract, modified ryegrass pollen allergens carrying amino acid substitutions (mut 2) or truncations (mut3) at the C terminus of Lol p5 fail to reduce

IgE binding while mutations in domain D3 (mut 5) resulted in variable changes of IgE binding depending on the sera used (See page 273, col. 1, in particular). Thus the effects of these changes to the polypeptide of any protein allergen are largely unpredictable.

With respect to the Astwood et al reference (J Allergy Clin Immunol January 2000), the abstract merely states that the authors have identified the major and minor IgE binding epitopes of potato allergen and have identified within these IgE epitopes the amino acid residues that when substitute would reduce or abolish IgE binding to these peptides. However, the abstract does not discloses the structure of the modified food allergen.

With respect to the Helm et al reference (J. Allergy Clin Immunol 105: 378-84, Feb 2000), the state of the prior art as exemplified by Helm et al is such that determining which amino acid within the IgE epitope when mutated would reduced IgE binding is empirical by nature and the effect of amino acid substitution is unpredictable. Helm et al teach that alanine substitutions in IgE epitope 6 at amino acid position 6 and 7 and epitope 16 at position 7 showed reduced IgE binding. However, IgE epitopes 1, 13 and 15 could not be mutagenized to a non-IgE-binding peptide with alanine substitution at any position in the peptide with serum from patients (See col. 2, paragraph bridging page 380 and 381, col. 1, page 381, in particular). Thus the effects of these changes to the polypeptide of any food allergen are largely unpredictable.

With respect to the Ayuso et al reference (J Allergy Clin Immunol January 2000), the abstract states that there are five major IgE binding regions of shrimp allergen Pen a1 (region 1: 43-57, region 2: 85-105, region 3: 133-153, region 4: 187-201 and region 5: 247-284). The abstract further states that amino acid substitutions in the center of the IgE epitope sequence are more likely to eliminate IgE binding by 59.5% as compared to substitutions in the peripheral parts of the epitope (39.1%), which means that approximately 40% of the chance that amino acid substitution in the center of the IgE epitope sequence has no effect or increase IgE binding, and approximately 60% the chance that substitutions in the peripheral parts of the epitope has no effect or increase IgE binding. The abstract further states that single amino acid non-conservative amino acid substitution in the center of the IgE epitope are most likely to reduce or abolish IgE antibody binding (63.5%) as compared to 23.1% conservative substitution, which means that approximately 36.5% of the chance that the non-conservative amino acid substitution has no effect or increase IgE binding. Thus the effects of these changes to the polypeptide of any food allergen are largely unpredictable.

With respect to the Lehrer et al reference, Lehrer et al teach that one amino acid substitution may have no effect, reduced or abolished IgE binding, or even enhanced IgE binding. This certainly has signification implications when assessing IgE antibody reactivity to food allergen epitopes. Generally, greater than two substitutions usually abolished IgE-binding ability to modified shrimp allergen Pen a 1 peptides (IgE epitopes) (See page 79, last paragraph, in particular). Lehrer et al echo the teachings of Ayuso et al that substitutions from the epitope center are more likely to eliminate (59.5% IgE binding) as opposed to substitutions on the epitope periphery (39.1%) discussed earlier. (See paragraph-bridging page 79 and 80, in particular). Lehrer et al teach "whether these observations for IgE binding epitopes of tropomyosin from shrimp are relevant to those other food allergens *is not clear*. Generally, our results are consistent with those reported of major peanut allergens Ara h1, 2, and 3[37-39]." (See page 80, paragraph 1, in particular). To paraphrase the teachings of Burks et al on the mutagenesis of IgE epitope in Ara h1, "there is no obvious position within each IgE epitope that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, Eur. J. Biochem 245: 334-339, 1997 in particular). To paraphrase the teachings of Stanley et al on the mutagenesis of IgE epitope in Ara h2, each IgE epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each IgE epitope peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding (See page 251, Arch. Biochem. Biophys. 342(2): 244-253, 1997, in particular). Thus the effects of these changes to the polypeptide of any food allergen, the corresponding polynucleotide encoding the modified allergen are largely unpredictable. Given the unlimited number of modified protein allergen, modified food allergen, and any modified peanut allergens, the limited amount of guidance as to which amino acid residue(s) in the at least one IgE epitope essential for IgE antibody binding in all protein and food allergen to be modified by substitution, deletion, addition or combination thereof, the lack of sufficient working examples in the specification as filed, and the unpredictability in the art as discussed supra, it would require undue experimentation of one skilled in the art to practice the full scope of claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Until the structures of the modified protein allergen, and modified food allergen have been

identified, the specification merely extends an invitation for one skill in the art to further experimentation to arrive at the claimed invention.

At paragraph bridging page 11-12 of the Brief, Appellant asserts that the Examiner's argument fail to establish a case of lack of enablement, Appellant argues the Examiner fails to recognize that even though the possibility exists that the initial modification of IgE binding epitopes may not identify suitable modified proteins, as was the case in Wands and also in Burks et al., Stanley et al. and Fasler et al.), practitioners would be prepared to test more than one modification and to screen for useful modified proteins. The present case need only meet the enablement standard that was set in Wands. Appellant respectfully submits that the standard has been met, reconsideration and withdrawal of the rejection for lack of enablement is therefore requested.

Appellant's arguments have been fully considered but are not found to be persuasive. It is noted that the pending claims are not drawn to a method of making modified protein allergen or food allergen. The scope of claims 37-51, 53 and 65-71 (Group A) encompasses any modified protein allergen. The scope of claims 60-62 and 65-71 (Group B) encompasses any modified food allergen, such as modified allergens from legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, codfish, hazel nut, and shrimp. The scope of claims 63-64 and 65-71 (Group C) encompasses any modified peanut allergens.

The specification discloses only three peanut allergens Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) as depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification discloses only three modified peanut allergens Ara h1, Ara h2 and Ara h3. The modified peanut allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M (page 24). The specification discloses a second modified peanut allergen Ara h2 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted

for alanine, and a third modified peanut allergen Ara h3 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy. The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a *reduced* IgE binding. In contrast, substituting alanine for arginine of Ara h1 leads to an *increased* IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type (unmodified peanut allergen) but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

Besides the specific modified peanut allergen as shown on page 24, there is insufficient guidance as how to make all modified protein allergens, all modified food allergens from legumes, milks, grains, eggs, fish, crustaceans, mollusks, such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp whose amino acid sequence is "substantially" identical to any unmodified protein allergen or any food allergen because there is a lack of guidance as to which amino acid within which IgE epitope of the full length unmodified protein allergen or food allergen to be substituted for which amino acids, to be deleted or to be added and whether the resultant modified protein allergen reduces IgE binding, retains the ability to bind IgG and/or initiate a Th1-type response. The specification does not define the term "substantially". A modified protein allergen could be 50% identical to unmodified protein would still be "substantially identical" to that of unmodified protein allergen. The term "at least one" has no upper limit as to how many amino acid residues could be modified by substitution, deletion, addition and combination thereof, much less which amino acid within which IgE epitope (since allergens has more than one IgE epitomes) within the full length protein allergen could be substitute for which undisclosed amino acid residue. Given the unlimited number of undisclosed protein allergen and food allergens, there is insufficient working examples demonstrating that any

modified protein allergen after modification by substitution, deletion, addition would retain the ability to activate T cells, bind IgG and initiate a Th-1 type response, much less binding to IgE for treating any allergy. Until the amino acid critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding or within the full length polypeptide in all unmodified protein allergen, and all unmodified food allergen and all peanut allergens other than Ara h1, 2, 3 have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described, it would require an undue amount of experimentation for one of skill in the art to arrive at the scope of the claimed invention. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment. Since the modified protein allergen mentioned above is not enabled, it follows that the composition comprising said modified protein allergen and adjuvant is not enabled. It also follows that any undisclosed modified protein allergen made in a transgenic plant or animal or recombinant host are not enabled.

Even if the specific peanut food allergen is recited in claim 64, only the specific amino acid substitution within the full length of SEQ ID NO: 1 and 2 such as the ones disclosed on page 24, lines 16-24 or the ones shown in page 24, Table 4-6 have reduced IgE binding less than 1% of that observed to the unmodified peanut allergens. Given the indefinite number of undisclosed modified protein allergen and modified food allergen, it is unpredictable which undisclosed modified protein allergen and food allergen would reduce IgE binding, activate T cells and/or bind IgG, in turn, would be useful for immunotherapy. There is no recognition in the art that sequence identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Fasler *et al.* (of record, PTO 892) teach modified protein allergen derived from house dust mite Der p1 that has been modified by amino acid substitutions at positions 173, 175, 176, 180 and 181 for alanine or glycine. However, these modified protein allergen fail to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al* further teach that substituting a neutral amino acid residue such as Asn at position 173 for either a basic residue such as Lysine, or a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180

and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al.* (of record, PTO 1449) teach a modified food allergen from peanut such as Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine. The modified peanut allergen reduces IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* (of record, PTO 1449) teach a modified food allergen from peanut such as Ara h2 by amino acid substitution with alanine at position 67, 68 or 69. The modified peanut allergen having alanine substitution at position 67, 68 and 69 significantly reduced IgE binding. In contrast, substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al* (of record, PTO 892) teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al* (of record, PTO 892) teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular). Thus the effects of these changes to the polypeptide of any food allergen, the corresponding polynucleotide encoding the modified allergen are largely unpredictable. Given the unlimited number of modified protein allergen, modified food allergen, and any modified peanut allergens, the limited amount of guidance as to which amino acid residue(s) in the at least one IgE epitope are essential for IgE antibody binding, the lack of sufficient working examples in the specification as filed, and the unpredictability in the art as discussed supra, it would require undue experimentation of one skilled in the art to practice the full scope of claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d

1334 (PTO Bd. Pat App. & Inter. 1992). Consequently, Appellant has not provided sufficient guidance to enable one of ordinary skill in the art to make all modified protein allergen, all modified protein allergen without the amino acid sequence, as encompassed by the scope of the claims. Until the structures of the modified protein allergen and modified food allergen have been identified, the specification merely extends an invitation for one skill in the art to further experimentation to arrive at the claimed invention.

Claim Rejections - 35 USC § 112 written description

At page 12 of the Brief, Appellant submits that the claims of Group A stand or fall together; the claims of Group B stand or fall together; and the claims of Group C stand or fall together. By definition, claim groups that cover species of different scope require a separate written description and/or different levels of written description. Since claim groups A-C cover species of different scope (i.e., modified protein allergens, modified food allergens and modified peanut allergens), these claim groups must be considered separately and stand or fall separately for purposes of this rejection.

Appellant's arguments have been fully considered but are not found to be persuasive. It is the examiner's position that the written description rejections of claims 37-51, 53 and 65-71 should stand or fall together because claims 65-71 are in Groups A, B and C. Further, a species anticipates a genus.

At second paragraph bridging page 12 of the Brief, Appellant submits that there is a strong presumption that claims submitted with an application are adequately described by the application. Claim 37, 40-51 and 53 were present in substantially the same as claims 14-29 in the application as originally filed. Added claims 60-64 paralleled the language of claim 37 and are of narrower scope (i.e., they are simply limited to food or peanut allergens). Added claims 65-70 are dependent claims and recite the limitations found in original claim 14 and the data of Table 6 of the specification as filed (see discussion under Issue # 3 below). Added claim 71 is a dependent claim and recites a limitation found in the section spanning pages 24-25 of the specification as filed.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. In contrast to appellant's assertion that limitations of Claim 37, 40-51 and 53 were substantially the same as claims 14-29 in the application as originally filed, original claim

14 recites "A modified allergen which is less reactive with IgE comprising at least one IgE binding site present in the allergen modified by at least one amino acid change r having at least one amino acid bound by a compound so that the site no longer binds IgE, wherein the modified allergen activates T cells". Instant claim 37 recites A modified protein allergen whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein allergen, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified protein allergen.

In contrast to appellant's assertion that added claim 71 is a dependent claim and recites a limitation found in the section spanning pages 24-25 of the specification as filed, claim 71 encompasses any modified protein allergen, any modified food allergen any modified peanut allergen wherein binding by serum IgE to the at least one epitope is reduced for the modified allergen to less than about 1% of that observed to the unmodified allergen. Pages 24-25 of the specification discloses only modified *peanut allergen Ara h1 peptide* that resulted in less than 1% of IgE binding compared to wild type peptide (see paragraph bridging page 24 and 25).

The specification discloses only three peanut allergens Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) as depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification discloses only three modified peanut allergens Ara h1, Ara h2 and Ara h3. The modified peanut allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M (page 24). The specification discloses a second modified peanut allergen Ara h2 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and a third modified peanut allergen Ara h3 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino

acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy. The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a *reduced* IgE binding. In contrast, substituting alanine for arginine of Ara h1 leads to an *increased* IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type (unmodified peanut allergen) but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

With the exception of the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 mentioned above, there is insufficient written description about the structure without the amino acid sequence of *all* modified protein allergen, *all* modified food allergen and *all* modified peanut allergen other than Ara h1, 2 and 3. The specification does not provide a description of structural features that are common to IgE epitopes other than the peanut allergens specifically exemplified. In fact, the specification discloses that IgE epitopes of peanut allergens shared no common amino acid sequence motif (See Table 4-6 on page 26-27). The specification does not provide a description of polypeptide of all modified protein allergen, and polypeptide of all modified food allergen other than the peanut allergens specifically exemplified. Neither the specification's description of exemplary modified IgE epitopes from only three peanut allergens nor its general description of how those skilled in the art could find other IgE epitopes to make other modified protein allergen, modified food allergen and modified peanut allergen (claim 63) is adequately to described the genus defined by claims 37, 60 and 63. With regard to the term "substantially identical", the specification does not defined the term "substantially identical". A modified protein allergen could be 50% identical to unmodified protein would still be "substantially identical" to that of unmodified protein allergen. Further, the term "at least one" has no upper limit as to how many amino acid residues could be modified by substitution, deletion or addition, much less which amino acid to be substituted for which amino acid within which IgE epitope

(since allergens has more than one IgE epitomes) and within the full length of all protein allergens, all food allergens and all peanut allergens.

Until the amino acid critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding or within the full length polypeptide in all modified protein allergen, all modified food allergen and all peanut allergens other than Ara h1, 2, 3 have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described, the modified protein allergen, and the modified food allergen obtained from a source selected from the group consisting of legumes other than peanut, milks, grains, eggs, fish, crustaceans and mollusks, wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp are not adequately described. Since the structure of the modified protein allergen (claims 37), the structure of modified food allergen (claim 60) and the structure of modified peanut allergen other than Ara h1, 2, and 3 (claim 63) have not been adequately described, it follows that the modified protein allergen that retains the ability to activate T cells (claim 43), or binds IgG (claim 44), or retains the ability to initiate a Th1 type response (claim 45) are not adequately described. It also follows that the composition comprising the undisclosed modified protein allergen and the adjuvant such as the ones recited in claim 47 is not adequately described. Since the structure such as the amino acid sequence of all modified food allergen is not adequately describe, it follows that the modified protein expressed in a recombinant host such as the ones recited in claims 49-50 are not adequately described.

Even if the modified peanut allergen is limited to Ara h1, Ara h2 and Ara h3 (claim 64), there is insufficient written description about the structure of said modified allergens without reciting the amino acid sequence in the claim.

The specification discloses only three modified food allergens from only peanut. Given the lack of a written description of *any* additional representative species of modified protein, modified food allergen from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, codfish, hazel nut soybean and shrimp, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

At page 13-14 of the Brief, appellant argues whether written description requirement ever be satisfied for the claims relating to nucleotide molecules or protein unless the complete sequence is explicitly set forth in the specification and recited in the claim by way of a SEQ ID NO. The Examiner has rejected claim 63 on the ground that Appellant is only entitled to claim full length peanut allergens Ara h1, 2 and 3 that have been modified by substitution with alanine or methionine at those specific locations listed in Tables 4, 5, and 6. The specification discloses complete amino acid sequences of Ara h1, 2 and 3 (SEQ ID NO: 2, 4, and 6), and also the nucleotide sequences of genes that encode them (SEQ ID NO: 1, 3 and 5). The specification further sets out the amino acid sequences of each 23 IgE epitopes mapped in the Ara h1 protein (Table 1), the amino acid sequence of each 10 IgE epitopes mapped in the Ara h2 protein (Table 2) and the amino acid sequence of each of 4 epitopes mapped in the Ara h3 protein (Table 3). One skilled reading the specification, would understand, indeed would explicitly be told that the presented substitutions were merely exemplary and others would work as well.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The scope of claims 37-51, 53 and 65-71 (Group A) encompasses any modified protein allergen. The scope of claims 60-62 and 65-71 (Group B) encompasses any modified food allergen, such as modified allergens from legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, codfish, hazel nut, and shrimp. In contrast to appellant's assertion that claim 63 is limited to modified peanut allergen Ara h1, 2 and 3, the scope of claim 63 (Group C) encompasses any modified peanut allergens.

The specification discloses only three peanut allergens Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) as depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification discloses only three modified peanut allergens Ara h1, Ara h2 and Ara h3. The modified peanut allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A;

P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M (page 24). The specification discloses a second modified peanut allergen Ara h2 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and a third modified peanut allergen Ara h3 whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy. The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a *reduced* IgE binding. In contrast, substituting alanine for arginine of Ara h1 leads to an *increased* IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type (unmodified peanut allergen) but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

With the exception of the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 mentioned above, there is insufficient written description about the structure without the amino acid sequence of *all* modified protein allergen, *all* modified food allergen and *all* modified peanut allergen other than Ara h1, 2 and 3. The specification does not provide a description of structural features that are common to IgE epitopes other than the peanut allergens specifically exemplified. In fact, the specification discloses that IgE epitopes of peanut allergens shared no common amino acid sequence motif (See Table 4-6 on page 26-27). The specification does not provide a description of polypeptide of all modified protein allergen, and polypeptide of all modified food allergen other than the peanut allergens specifically exemplified. Neither the specification's description of exemplary modified IgE epitopes from only three peanut allergens nor its general description of how those skilled in the art could find other IgE epitopes to make other modified

protein allergen, modified food allergen and modified peanut allergen (claim 63) is adequately to described the genus defined by claims 37, 60 and 63. With regard to the term "substantially identical", the specification does not defined the term "substantially identical". A modified protein allergen could be 50% identical to unmodified protein would still be "substantially identical" to that of unmodified protein allergen. Further, the term "at least one" has no upper limit as to how many amino acid residues could be modified by substitution, deletion or addition, much less which amino acid to be substituted for which amino acid within which IgE epitope (since allergens has more than one IgE epitomes) and within the full length of all protein allergens, all food allergens and all peanut allergens.

Until the amino acid critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding or within the full length polypeptide in all modified protein allergen, all modified food allergen and all peanut allergens other than Ara h1, 2, 3 have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described, the modified protein allergen, and the modified food allergen obtained from a source selected from the group consisting of legumes other than peanut, milks, grains, eggs, fish, crustaceans and mollusks, wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp are not adequately described. Since the structure of all modified protein allergen (claims 37), the structure of all modified food allergen (claim 60) and the structure of modified peanut allergen other than Ara h1, 2, and 3 (claim 63) have not been adequately described, it follows that the modified protein allergen that retains the ability to activate T cells (claim 43), or binds IgG (claim 44), or retains the ability to initiate a Th1 type response (claim 45) are not adequately described. It also follows that the composition comprising the undisclosed modified protein allergen and the adjuvant such as the ones recited in claim 47 is not adequately described. Since the structure such as the amino acid sequence of all modified food allergen is not adequately describe, it follows that the modified protein expressed in a recombinant host such as the ones recited in claims 49-50 are not adequately described.

Even if the modified peanut allergen is limited to Ara h1, Ara h2 and Ara h3 (claim 64), there is insufficient written description about the structure of said modified allergens without reciting the amino acid sequence in the claim.

The specification discloses only three modified food allergens from only peanut. Given the lack of a written description of *any* additional representative species of modified protein, modified food allergen from legumes other than peanut, milks, grains, eggs, fish, crustaceans,

mollusks, wheat, barley, codfish, hazel nut soybean and shrimp, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

At page 15-16 of the Brief, Appellant argues that claim 60 recites "A modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen". Once again, the Examiner is correct that the specification does not explicitly set out the sequence of every modified food allergen that falls within the scope of claim 60. On the other hand, the specification does explicitly set out the sequence of several examples of modified peanut allergens. These modified peanut allergens are described as "exemplary" of the inventive principles. For Example, the specification recites that "Peanut allergens (Ara h1, Ara h2, and Ara h3) have been used in the examples to demonstrate alteration of IgE binding sites while retaining binding to IgG and activation of T cells (page 4, lines 15-17). The specification also points to several other common food allergens (see page 8, lines 1-3). The specification provides references for food allergens whose IgE epitomes had already been identified (See page 8, lines 4-13). The specification also describes techniques for modifying sequences within IgE sites (see page 10, lines 3-6 and Examples 2-3) and identifying those modifications that reduce IgE binding (see page 9, lines 24-28 and examples 1-2). The specification provides evidence that the inventive strategy successfully produced modified peanut allergens with reduced IgE reactivity. A person skill in the art would immediately understand the implications of the inventive exemplification of reduced-allergenicity peanut allergens. Those of ordinary skill in the art will immediately appreciate the inventors were in possession of the claimed invention.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The scope of claims 60-62 and 65-71 (Group B) encompasses any modified food allergen, such as modified allergens from legumes other than peanut allergen, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, codfish, hazel nut, and shrimp. As conceded by Appellant, the Examiner is correct that the specification does not explicitly set out the sequence of every modified food allergen that falls within the scope of claim 60. The specification discloses only three peanut allergens Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27) as discussed supra.

The specification does not provide a description of amino acid sequence of all modified food allergen other than the peanut allergens specifically exemplified. Neither the specification's description of exemplary modified IgE epitopes from three peanut allergens nor its general description of how those skilled in the art could predict which other amino acids are critical in the IgE binding epitope to make into modified food allergen is adequately to described the genus defined by claim 60. Until the amino acid critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding within the full length polypeptide in all food allergen have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described; in essence, the specification simply directs those skilled in the art to go figure out themselves what the claimed modified protein allergen look like. Thus, the specification's disclosure is inadequate to describe the claimed genus of modified food allergen. Further, the specification discloses only three modified peanut allergens Ara h1, Ara h2 and Ara h3 from only peanut (Arachis hypogaea). Given the lack of a written description of *any* additional representative species of modified protein, modified food allergen from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, codfish, hazel nut soybean and shrimp, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

At page 16-17 of the Brief, Appellant argues that although the claims in Group A are broader, there is no failure of written description. The specification makes clear that the

inventive principles are applicable to any allergen (see, for example, page 4, lines 2-14; page 7, line 26 to page 9, line 15; and page 29, lines 18-20). The specification also specifically lists a variety of relevant allergens (see, for example, page 8, lines 13-16: other allergens include proteins from insects such as flea, tick, mite, fire ant, cockroach, and bee as well as molds, dust, grasses, trees, weeds, and proteins from mammals including horses, dogs, cats, etc."). The specification includes extensive discussion of latex allergens, in particular, and provides references reporting IgE epitopes within these allergens (see, for example, page 8, line 19-page 9, line 15). The specification further recites the specific modifications of claims 38-42 (e.g., see page 4, lines 17-23 and the Examples) and the properties of claims 43-45 (e.g., see page 4, lines 8-14 and 26-28). The specification also specifically recites relevant subsets of antigens recited in claims 51 and 60-62 (e.g., pages 7-9 and the Examples). Likewise, the specification specifically points to adjutants having the characteristics recited in claim 47 (e.g., see page 15, lines 19-20) and to recombinantly prepare modified allergens as recited in claims 48-50 (e.g., see page 12 and Example 3). The steps of claim 53 are described on pages 9-10 and in the Examples.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The scope of claims 37-51, 53 and 65-71 (Group A) encompasses any modified protein allergen. The specification as filed does not provide adequate written description support for all modified protein allergen. The specification discloses only three modified peanut allergens Ara h1, Ara h2 and Ara h3 that have been discussed supra. The specification merely lists a variety of allergens (see, for example, page 8, lines 13-16: other allergens include proteins from insects such as flea, tick, mite, fire ant, cockroach, and bee as well as molds, dust, grasses, trees, weeds, and proteins from mammals including horses, dogs, cats, etc."), including latex allergens, in particular, and provides references reporting IgE epitopes within these allergens (see, for example, page 8, line 19-page 9, line 15). However, none of these are modified allergens. The skilled artisan can envision neither all the contemplated amino acid sequence possibilities of the other modified protein allergen, nor the functions of the modified protein allergen. Consequently, conception in either case cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself of modified food allergen is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In

Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

The specification does not provide a description of amino acid sequence of all modified food allergen other than the peanut allergens specifically exemplified. Neither the specification's description of exemplary modified IgE epitopes from three peanut allergens nor its general description of how those skilled in the art could predict which amino acids are critical in the IgE binding epitope to make into modified protein allergen is adequately to described the genus defined by claim 37. Until the amino acid critical to IgE binding within the at least one IgE epitope essential for IgE antibody binding or within the full length polypeptide in all protein allergen have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described; in essence, the specification simply directs those skilled in the art to go figure out themselves what the claimed modified protein allergen look like. Thus, the specification's disclosure is inadequate to describe the claimed genus of modified food allergen. Further, the specification discloses only three modified protein allergens Ara h1, Ara h2 and Ara h3 from only peanut (Arachis hypogaea). Given the lack of a written description of *any* additional representative species of modified protein, modified food allergen from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, codfish, hazel nut soybean and shrimp, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Claim Rejections - 35 USC § 112 New Matter

At page 17 of the Brief, appellant summits that claims 59-60 recite a modified protein allergen that comprises at least one IgE epitope with 1-6, 1-5, 1-4, 1-3 or 1-2 modified amino

acid residues. Appellant submits that claims 56-69 stand or fall together. Appellant submits that these claims are fully supported by the specification and claims as originally filed. In particular, original claim 14 reads "a modified allergen [...] comprising at least one IgE binding site (. . .) modified by at least one amino acid change (.. .)." Original claim 14 therefore makes it perfectly clear that the present invention encompasses modified protein allergens with at least one IgE binding site that includes more than one modified amino acid residue. The specification as filed further teaches IgE epitopes that include 1, 2, 3, 4, 5 or 6 amino acid residues that, when altered, lead to a reduction in IgE binding (e.g., see epitopes 5, 7, 8, 9, 18 in Table 4 and epitope 4 in Table 6, respectively). The specification and claims as originally filed therefore clearly support the language of pending claims 65-69.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. Instant Claims 65-69 encompass any modified protein allergen or any modified food allergen and any modified peanut allergen wherein the at least one IgE epitope contains 1-6 (claim 65), 1-5 (claim 66), 1-4 (claim 67), 1-3 (claim 68), 1-2 (claim 69) amino acid residues that are modified as compared with the unmodified protein allergen, unmodified food allergen or unmodified peanut allergen. Original claim 14 recites "a modified allergen which is less reactive with IgE comprising at least one IgE binding site present in the allergen modified by at least one amino acid change or having at least one amino acid bound by a compound so that the site no longer binds IgE, wherein the modified allergen activates T cells".

The specification discloses only the specific modified peanut allergen Ara h1, 2, and 3 wherein the IgE epitopes that include 1, 2, 3, 4, 5 or 6 amino acid residues that, when altered, lead to a reduction in IgE binding (e.g., see epitopes 5, 7, 8, 9, 18 in Table 4 and epitope 4 in Table 6, respectively). Thus the original claim 14 and the specification do not have support for all modified protein allergen, all modified food allergen and all peanut allergen wherein "1-6", "1-5", "1-4", "1-3", and "1-2" amino acid residues that have been modified in the at least one IgE epitope. Appellant has not pointed out the support for said "1-6, 1-5, 1-4, 1-3 and 1-2 amino acid residues" in any modified protein allergen, and any modified food allergen other than the specific peanut allergen shown in Table 4-6 of the specification. Even if the claims are limited to modified peanut allergens, the specific "1-6", "1-5", "1-4", "1-3" and "1-2" have no support in the specification as filed.

Claim Rejections - 35 USC § 112 Second paragraph

At page 18 of the Brief, appellant summits that claims 37, 60 and 63 stand or fall together. Appellant submits that the nature of the presently claimed invention is such that minor variations from an otherwise identical amino acid sequence (e.g., the addition of a single terminal methionine during recombinant synthesis) could be made without losing the benefit of the present invention. One skilled in the art, upon reading the present specification, would readily recognize such trivial variations.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. In contrast to appellant's argument that the nature of the presently claimed invention is such minor variations from an otherwise identical amino acids sequence, the specification does not define the term "substantially". A modified protein allergen (claim 37), a modified food allergen (claim 60) or a modified peanut allergen (claim 63) having 50% sequence identity to unmodified protein would still be "substantially identical" to the unmodified protein allergen. Thus one of ordinary skill in the art cannot appraise the scope of the claimed invention.

Claim Rejections - 35 USC § 102(b)

Claims 37-39, 41-46, 48-51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,547,669 (Aug 1996, PTO 892).

At page 19-20 of the Brief, appellant summits that claims 37-39, 41-46, 48-51 and 53 stand or fall together. Appellant submits that the "recombitope peptides" that are taught by U.S. Pat. 5,547,669 cannot anticipate these claims since they do not satisfy the limitations of every claimed element. In particular, one skilled in the art would immediately recognize that a recombitope peptide" does not have an amino acid sequence that is substantially identical to that of an unmodified allergen except that at least one amino acid has been modified in at least one IgE epitope." In general, the combitope peptides" are peptides that include at least two T-cell epitopes derived from the same or from different protein antigens (e.g., see Abstract). It is presumably undisputed that a recombitope peptide" that includes T-cell epitopes derived from different protein antigens will necessarily have an amino acid sequence that bears no resemblance whatsoever to the amino acid sequence of either parent antigen. Further, when the T-cell epitopes are from the same protein antigen we are taught that these should be arranged in a noncontiguous configuration (see lines 3-8, column 7, emphasis added) and a nonsequential order (e.g., see lines 8-14, column 7, emphasis added). In order to reduce the likelihood of IgE binding,

IgE epitopes are preferably excluded from the amino acid sequences of the recombitope peptides" see lines 8-14, column 7, emphasis added). Again it is presumably undisputed that these recombitope peptides" will also have an amino acid sequence that bears no resemblance to the amino acid sequence of the parent antigen. As the foregoing sections highlight, U.S. Pat. 5,547,669 teaches methods that involve extracting, rearranging and pasting T-cell epitopes that were originally present in one or more natural protein antigens. IgE epitopes are preferably extracted and removed entirely. The resultant "recombitope peptides" are wholly artificial peptides that bear no resemblance whatsoever to their parent antigens. U.S. Pat. 5,547,669 therefore teaches strongly away from modified protein allergens whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope of the unmodified protein allergen, as recited in the present claims. The substitutions, deletions, or additions that are referred to by the Examiner (e.g., lines 1-5, 15-17 and 59-62, column 15) do not remedy these deficiencies, if anything they further differentiate "recombitope peptides" from the claimed invention. U.S. Pat. 5,547,669 do not anticipate or render obvious claims 37-39, 41-46, 48-51 and 53.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. As discussed supra, a modified protein allergen having 50% sequence identity to any unmodified protein would still be "substantially identical" to the unmodified protein allergen. A recombinant peptide that bears little resemblance whatsoever to their parent antigen would still be "substantially identical" to the parent unmodified protein allergen since the specification does not define the term what is meant by "substantially identical". Further, it is noted that none of the claims recite a particular amino acid sequence for any modified protein allergen, any modified food allergen and any modified peanut allergen. Further, the term "modified" includes addition, deletion, substitution and combination thereof. The '669 patent teaches modified protein allergen by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). In fact, the specification discloses alanine substitution (See page 24, line 11-18, in particular). The term "at least one amino acid has been modified" makes it clear that more than one modified amino acid residues in the modified protein allergen.

The '669 patent teaches a modified protein allergen such as FEL DI from cat which is a mammal, whose amino acid sequence is substantially identical to that of an unmodified protein

allergen and that the modified protein has reduced IgE binding (See column 3, lines 36-45, in particular). The reference modified protein allergen (recombitope peptide) is a portion of the unmodified protein allergen from cat produced by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). The reference modified protein allergen is expressed recombinantly in host cell such as bacteria (E coli), and the reference modified protein allergen stimulates T cell activity such as T cell proliferation better than unmodified protein allergen (See column 24, lines 8-67, bridging column 25, lines 1-32, in particular), initiates delayed type sensitivity which is Th-1 response (See column 26, lines 60-62, in particular) and reduces IgE binding (See column 22, lines 44, column 23, lines 59-61, in particular). Claims 48-49 are included in this rejection because a product is a product, irrespective of how it is made. The recitation of a process limitation in claim 48-49 is not seen as further limiting the claimed product, since multiple processes can make equivalent products. The reference modified protein allergen inherently has the ability to bind IgG since the reference modified protein is modified the same way as that of the specification on page 24 such as substituting neutral amino acid alanine (See column 15, lines 1-5, 15-17) or hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62 of '669, in particular). Since the Patent Office does not have the facilities for examining and comparing the modified protein allergen of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the antibodies of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The '669 patent further teaches a method for designing recombitope peptides of any allergen where the protein antigen to which the individual is senstive has unknown or ill-defined epitope (See abstract, in particular) and the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular). Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 102(a)

Claims 37, 60-61 and 63-71 are rejected under 35 U.S.C. 102(a) as being anticipated by Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449; see entire document).

At page 20, second paragraph of the Brief, Appellant submits that the teachings of Burks (1997) were included near verbatim in U.S. Serial No. 08/717,933 filed September 23, 1996 (see

pp. 133-155 and the Figures referred to therein). The present application properly claims priority to this 1996 filing. Burks (1997) was published after this priority date and cannot therefore be used as prior art under 35 U.S.C. § 102(a).

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. Appellant's attempt to broadening out the scope of the claims and the continuous updating page 1 of the specification to finally claim priority to 08/717,933 (filed Sept 23, 1996) is acknowledged. However, the filing date of the instant claims 37, 60-61 and 65-71, is deemed to be the filing date of instant application while the filing date of instant claims 63-64 is deemed to be the filing date of the priority application 60/073,283, 60/074,633, 60/074,624, 60/074,590 that all filed Feb 13, 1998 because (1) the 08/717,933 application filed Sept 23, 1996 discloses only the specific modified peanut allergen Ara h1, and Ara h2 (page 194), monoclonal antibody specific to a selected peanut allergen, hybridoma and immunoassay to be used for determining the concentration of a specific allergen (Ara h I) (See summery of invention, pages 6-12, claims of 08/717,933, in particular). (2) The USSN 08/717,933 does not support the claimed limitations of any modified protein allergen (claims 37-51), any modified food allergen (claims 60-62), any modified peanut allergen other than Ara h1 and 2 (claim 63), the modified Ara h3 allergen (claim 64), the "1-6 amino acid residues" of any modified protein allergen or any modified food allergen (claim 64), the "1-5 amino acid residues" of any modified protein allergen or any modified food allergen (claim 66), 1-4 amino acid residues" of any modified protein allergen or any modified food allergen (claim 67), 1-3 amino acid residues" of any modified protein allergen or any modified food allergen (claim 68), the "1-2 amino acid residues" of any modified protein allergen or any modified food allergen (claim 69). (3) the priority applications 60/073,283, 60/074,633, 60/074,624, 60/074,590 all filed Feb 13, 1998 disclose only modified peanut allergen Ara h1, Ara h2 and Ara h3. Applicants are reminded that such priority for the instant limitations requires a written description and enablement under 35 U.S.C. § 112, first paragraph. Therefore, The filing date of the instant claims 37, 60-61 and 65-71, is deemed to be the filing date of instant application while the filing date of instant claims 63-64 is deemed to be the filing date of Feb 13, 1998.

Claim Rejections - 35 USC § 103(a)

Claims 37 and 47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) in view of Hoyne *et al* (of record, Immunology and Cell Biology 74: 180-186, 1996, PTO 892).

At page 20, last paragraph of the Brief, Appellant submits that claims 37 and 47 stand or fall together. The teachings of U.S. Pat. 5,547,669 and its deficiencies with regards to independent claim 37 have been discussed supra. Hoyne is cited solely as teaching certain elements added in dependent claim 47, specifically certain adjutants. The Examiner indicates no teaching or suggestion in Hoyne that could overcome the deficiencies of U.S. Pat. 5,547,669.

Appellant's arguments have been fully considered but are not found to be persuasive. As discussed supra, a modified protein allergen, a modified food allergen or a modified peanut allergen having 50% sequence identity to the unmodified protein would still be "substantially identical" to the unmodified protein allergen. A recombinant peptide that bears little resemblance whatsoever to their parent antigen would still be "substantially identical" to the parent unmodified protein allergen since the specification does not define the term what is meant by "substantially identical". Further, it is noted that none of the claims recite a particular amino acid sequence for any modified protein allergen, any modified food allergen and any modified peanut allergen. Further, the term "modified" includes addition, deletion, substitution and combination thereof. The '669 patent teaches modified protein allergen by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). The term "at least one amino acid has been modified" makes it clear that more than one modified amino acid residues in the modified protein allergen.

The teachings of the '669 patent have been discussed supra.

The claimed invention in claim 47 differs from the teachings of the reference only in that a composition comprising the modified allergen and an adjuvant such as IL-12, and IFNγ.

Hoyne *et al.* teach patients receiving the PLA-2 specific peptides from bee venom demonstrated a decrease in allergen specific IgE and a corresponding rise in IgG levels; most patients reported a significant improvement in clinical symptoms (See page 183, column 1, paragraph 2, in particular). Hoyne *et al.* further teach peptide-mediated regulation of allergic immune response and a successful desensitization using peptide-mediated immunotherapy is accompanied by a decrease Th2-type cytokine with a concomitant increase in IFNγ production

(See page 180, column 2, in particular). The reference further teaches that the key to successful immunotherapy may dependent on reprogramming the immune response by co-administering modified allergen peptide in the presence of adjuvant such as IL-12 or IFNγ (See page 183, column 2, paragraph 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate or combine any modified allergen as taught by the '669 patent with the IL-12 or IFNγ as taught by Hoynes et al because the key to a successful peptide-based immunotherapy depends on reprogramming the immune response by co-administering allergen peptide in the presence of IL-12 or IFNγ since IL-12 or IFNγ would down-regulate ongoing Th2 responses in vivo by suppressing IgE production as taught by Hoyne et al (See page 183, column 2, in particular).

Claim Rejections - 35 USC § 103(a)

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) in view of Burks *et al* (of record, J Allergy Clin Immunol 6-93(4): 743-50; 1994 PTO 1449).

At page 21 first full paragraph of the Brief, Appellant submits that the teachings of U.S. Pat. 5,547,669 and its deficiencies with regards to independent claim 37 have been discussed supra. Burks (1994) is a secondary reference that is cited solely as teaching unmodified protein allergens, namely peanut Ara h 1 and Ara h 2, and alleged IgE epitopes of these. Appellant notes that Burks (1994) does not teach IgE epitopes of Ara h 2 and only identifies the existence of three IgE epitopes of Ara h 1 based on an ELISA inhibition assay using monoclonal antibodies - the locations of these three IgE epitopes within the Ara h 1 amino acid sequence are not provided. Besides, even if Burks (1994) had taught the location of any IgE epitope of Ara h 1 and/or Ara h 2, the Examiner has failed to point to any teaching or suggestion in Burks (1994) that could overcome the aforementioned deficiencies of U.S. Pat. 5,547,669.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons.

In response to Appellant's argument that Burks (1994) does not teach IgE epitopes of Ara h 2, Burks et al teach Ara h1 and Ara h2 have been purified from peanuts (See page 749, col. 1, second paragraph, in particular). Burkes et al teach a method of how to identify IgE epitope of protein allergen such as Ara h1 based on an ELISA inhibition assay using monoclonal antibodies

(See page 744, Elisa inhibition, in particular). It is within the purview of one ordinary skilled in the art at the time the invention was made to identify other IgE epitope from other protein allergen such as Ara h2 as taught by Burks et al (1994). In fact, Appellant submits that there is no particular magic in the sequence of peanut or food allergens that makes these allergens more susceptible to mutations (page 11) and that other modified allergens with reduced IgE binding can also be made as evident by the teachings of the '669 patent.

In response to Appellant's argument that Burks et al does not teach the locations of these three IgE epitopes within the Ara h 1 amino acid sequence are not provided, it is noted that claim 37 does not recite the "locations of any IgE epitope within any amino acid sequence such as Ara h1 amino acid sequence". As discussed supra, a modified protein allergen, a modified food allergen or a modified peanut allergen having 50% sequence identity to unmodified protein would still be "substantially identical" to the unmodified protein allergen. A recombinant peptide that bears little resemblance whatsoever to their parent antigen would still be "substantially identical" to the parent unmodified protein allergen since the specification does not define the term what is meant by "substantially identical". Further, it is noted that none of the claims recite a particular amino acid sequence for any modified protein allergen, any modified food allergen and modified peanut allergen. Further, the term "modified" includes addition, deletion, substitution and combination thereof. The '669 patent teaches modified protein allergen by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). The term "at least one amino acid has been modified" makes it clear that more than one modified amino acid residues in the modified protein allergen. At minimum, at least one amino acid has been modified.

The '669 patent teaches a modified protein allergen such as FEL DI from cat whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that modified protein binding to IgE is reduced (See column 3, lines 36-45, in particular). The reference modified protein allergen (recombitope peptide) is a portion of the unmodified protein allergen from cat produced by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). In fact, the specification discloses allergen from cat (See page 8, line 16, in particular).

The claimed invention in claim 37 differs from the teachings of the reference only in that the modified protein allergen is peanut protein of Ara h1 and Ara h2.

Burks *et al* teach a major allergen of peanuts such as Ara h1 and the IgE binding specificity of Ara h1 antibodies is determined by competition ELISA using pooled peanut-specific IgE from patients allergic to the natural protein peanut allergen (See page 746, Table II, in particular). Burks et al further teach that the allergen is purified by affinity column chromatography and the Ara I allergen has a molecular weight of 63.5 kd and an isoelectric point of 4.55 while the second allergen such as Ara II has a molecule weight of 17 kd and an isoelectric point of 5.2 (See Abstract, page 749, column 1, first full paragraph, in particular). The reference further teaches that peanuts are considered one of the most allergenic food (See page 743, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cat allergen as taught by the '669 patent for the peanut allergen such as Ara h1 or Ara h2 as taught by Burks et al and modifying any one amino acid in the unmodified peanut allergen by alanine substitution as taught by '669 patent such that the modified peanut is no longer binds IgE as taught by the '669 patent for desensitization immune therapy. The amino acid that has been modified is obviously within the IgE epitope since the modified peanut allergen is now longer binds IgE. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify peanut allergen Ara h1 and Ara h2 because Burks *et al* teach peanuts are considered one of the most allergenic food (See page 743, column 1, in particular), the IgE binding epitope can be easily determined by IgE inhibition experiments using pooled peanut-specific IgE from patients allergic to the natural protein peanut allergen (See page 746, Table II, in particular) or monoclonal antibodies that bind specifically to Ara h 1 (See page 749, col. 1, Discussion, in particular). The '699 patent teaches that modified protein allergen with reduced IgE binding is useful for desensitize the individual to said protein allergen (See column 3, lines 34-36, in particular).

Claim Rejections - 35 USC § 103(a)

Claims 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) or Burks *et al* (Eur. J. Biochem. 245: 334-339; April 1997, PTO 1449) each in view of US Pat No. 5,449,669 (Sept 1995, PTO 892).

At page 21 last paragraph of the Brief, Appellant submits that claims 60-62 stand or fall together. The teachings of U.S. Pat. 5,547,669 and its lacking have been discussed supra. As discussed supra, Burks (1997) is not available as prior art under 35 U.S.C. j 103(a). U.S. Pat. No. 5,449,669 is cited solely as teaching an unmodified protein allergen, namely shrimp tropomyosin, and its two IgE binding epitopes. The Examiner points to no teaching or suggestion in U.S. Pat. 5,449,669 that could overcome the deficiencies of U.S. Pat. 5,547,669.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The Examiner disagrees for reasons discussed supra. A modified protein allergen, a modified food allergen or a modified peanut allergen having 50% sequence identity to unmodified protein would still be "substantially" identical to the unmodified protein allergen. A recombinant peptide that bears little resemblance whatsoever to their parent antigen would still be "substantially identical" to the parent unmodified protein allergen since the specification does not define the term what is meant by "substantially identical". Further, it is noted that none of the claims recite a particular amino acid sequence for any modified protein allergen, any modified food allergen and modified peanut allergen. Further, the term "modified" includes addition, deletion, substitution and combination thereof. The 5,547,669 patent teaches modified protein allergen by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). The term "at least one amino acid has been modified" makes it clear that more than one modified amino acid residues in the modified protein allergen. At minimum, the modified allergen has one amino acid that has been modified.

In contrast to appellant's argument that Burks (1997) is not available as prior art under 35 U.S.C. § 103(a), the Burks (1997) reference is a prior art because it is published in April 1997. The 08/717,933 application filed Sept 23, 1996 discloses only the specific modified peanut allergen Ara h1, and Ara h2 (page 194), monoclonal antibody specific to a selected peanut allergen, hybridoma and immunoassay to be used for determining the concentration of a specific allergen (Ara h I) (See summery of invention, pages 6-12, claims of 08/717,933, in particular).

The USSN 08/717,933 does not support the claimed limitations of any modified protein allergen (claims 37-51), any modified food allergen (claims 60-62), any modified peanut allergen other than Ara h1 and 2 (claim 63), the modified Ara h3 allergen (claim 64), the "1-6 amino acid residues" of any modified protein allergen or any modified food allergen (claim 64), the "1-5 amino acid residues" of any modified protein allergen or any modified food allergen (claim 66), 1-4 amino acid residues" of any modified protein allergen or any modified food allergen (claim 67), 1-3 amino acid residues" of any modified protein allergen or any modified food allergen (claim 68), the "1-2 amino acid residues" of any modified protein allergen or any modified food allergen (claim 69). The priority applications 60/073,283, 60/074,633, 60/074,624, 60/074,590 all filed Feb 13, 1998 disclose only modified peanut allergen Ara h1, Ara h2 and Ara h3. Therefore, The filing date of the instant claims 37, 60-61 and 65-71, is deemed to be the filing date of instant application while the filing date of instant claims 63-64 is deemed to be the filing date of Feb 13, 1998.

In contrast to appellant's assertion that the Examiner points to no teaching or suggestion in U.S. Pat. 5,449,669 that could overcome the deficiencies of U.S. Pat. 5,547,669, the teachings of the 5,547,669 patent and Burks *et al* (1997) have been discussed supra.

The invention in claim 61 differs from the teachings of the references only in that the unmodified protein allergen is obtained from crustacean.

The claimed invention in claim 62 differs from the teachings of the references only in that the unmodified protein allergen is obtained from shrimp.

The 5,449,669 patent teaches allergen obtained from unmodified food allergen such as shrimp, which is a member of crustacean family and IgE binding epitopes in shrimp (See abstract, in particular). The reference IgE epitopes are useful in diagnosis and/or treatment of allergies.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made substitute the cat allergen as taught by the 5,547,669 patent or the peanut allergen as taught by Burks et al for the food allergen such as shrimp as taught by the 5,449,669 patent and modifying at least one amino acid within the IgE binding epitopes of shrimp as taught by the 5,449,669 patent using the method as taught by the 5,547,669 patent or Burks *et al* for a modified food allergen that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified protein allergen as taught by the 5,547,669 patent and Burks et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the 5,449,669 patent teaches IgE epitopes from shrimp are useful in diagnosis and/or treatment of allergies. The 5,547,669 patent the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular). Burks *et al* teach that it is possible to mutate any allergen to a protein so that it no longer binds IgE for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Phuong Huynh
October 15, 2004

Conferees
Christina Chan
SPE, Art unit 1644

James Housel
SPE, Art unit 1648